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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,349	11/15/2001	Avi J. Ashkenazi	P2730P1C37	7811
35489	7590	06/16/2004	EXAMINER	
HELLER EHRMAN WHITE & MCAULIFFE LLP			BLANCHARD, DAVID J	
275 MIDDLEFIELD ROAD			ART UNIT	
MENLO PARK, CO 94025-3506			PAPER NUMBER	

1642

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,349	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 119-131 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 119-131 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>5/30/2002</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

1. The preliminary amendments filed 11/15/2001 and 9/30/2002 have been entered in full.
2. Claims 1-118 are cancelled.
3. Claims 119-131 have been added.
4. Claims 119-131 are pending and under examination.

Specification

5. The disclosure is objected to because of the following informalities:
 - a. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 307, line 28 and page 310, line 13. Applicant is required to check the entire disclosure and delete all the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01
 - b. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 119-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 119-131 are indefinite because the protein identified as PRO1159 (SEQ ID NO:377) is a soluble protein, and is not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed protein comprises an “extracellular domain” (for example see claim 119 parts (c) and (d)) is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of “the extracellular domain”...“lacking its associated signal sequence” (claim 119, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

b. Claim 131 is indefinite for reciting “epitope tag” because the exact meaning of the phrase is not clear. Does the phrase mean an “epitope” where an antibody binds or a tag that allows for purification that is an amino acid sequence that does not require binding to an antibody, or some other tag?

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 39-43, and 130-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80% amino acid sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the

Art Unit: 1642

absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the sequence set forth in SEQ ID NO:377 (i.e., PRO1159), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that

Art Unit: 1642

Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

10. Claims 119-124 and 129-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the cell line containing cDNA deposited under ATCC accession no. 203092. It is not clear whether the cDNA deposited as ATCC accession no. 203092 is known and publicly available or can be reproducibly isolated from nature without undue experimentation or is the same as SEQ ID NO:376 or encodes SEQ ID NO:377 or contains additional sequences in addition to SEQ ID NO:376.

Applicant's referral to the deposit of the cDNA on pages 563-566 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a

period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

11. Claims 119-123 and 130-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples,

Art Unit: 1642

6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a polypeptides having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:377 (i.e., PRO1159) or the extracellular domain thereof. There is no functional limitation in the claims as far as to the polypeptide. Applicants have taught the polypeptide consisting of the extracellular domain or, more accurately, the mature form of PRO1159, as well as the putative signal sequence (approximately amino acids 1-15 of PRO1159, see page 247, lines 7-8). This polypeptide is disclosed as having no sequence identities to any known proteins (see page 366; PRO1159). The specification discloses the polypeptide was positive for chondrocyte re-differentiation (Assay 110; see page 530). The specification does not teach an activity for the polypeptide or any active regions of the polypeptide. Thus one would not know if the polypeptide with the claimed homology would function as a polypeptide of PRO1159.

The claim encompasses an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. Since PRO1159 is a secreted protein, it would be expected that the mature form would be sufficient for function in the absence of the secretory signal. The functional domain of the protein is the mature form. Knowledge of the structure and function of PRO1159 does not provide predictability about function of a structurally related protein, even within the same class.

There are no working examples of polypeptides less than 100% identical to the PRO1159 polypeptide or the mature form thereof. The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification. Even if the claimed polypeptides had a function, the specification does not provide guidance for using polypeptides related to (*i.e.*, 80%-99% identity) but not identical to PRO1159. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

It is well known in the art that even a single modification or substitution in a protein sequence can alter the proteins function. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its

receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Priority

12. The examiner acknowledges the priority statement filed 9/3/2002, however, priority documents PCT/US00/05841, 09/380,137, PCT/US99/12252 and 60/095,285 do not support a substantial asserted utility or a well-established utility because these applications do not disclose the chondrocyte re-differentiation assay (Assay 110). Therefore, the instant claims are granted the priority date of PCT/US00/08439, 3/30/2000.

Claim Rejections

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

14. Claim 119-125 and 130-131 are rejected under 35 U.S.C. 102(a) as being anticipated by Rosen et al (PG-PUB US2002/0042386 A1, 1/31/2000).

The claims are interpreted as drawn to an isolated polypeptide having at least 80% amino acid identity to any region of the polypeptide sequence of SEQ ID NO:377, wherein the polypeptide is fused an epitope tag or an Fc region of an immunoglobulin.

Rosen et al teach a polypeptide sequence (SEQ ID NO:488) having 100% amino acid identity with residues 15-61 of the polypeptide of SEQ ID NO:377 (see the alignment attached to the back of this Office Action). Rosen et al teach chimeric polypeptides wherein the polypeptide is fused to the Fc region of an immunoglobulin (see page 107, paragraph 174).

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571)

Art Unit: 1642

272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER



LARRY R. HELMS, PH.D
PRIMARY EXAMINER

RESULT 507
US-09-764-870-488

; Sequence 488; Application US/09764870
; Patent No. US20020042386A1

; GENERAL INFORMATION:

; APPLICANT: Rosen et al.

; TITLE OF INVENTION: Nucleic Acids, Proteins, and Antibodies

; FILE REFERENCE: PT214

; CURRENT APPLICATION NUMBER: US/09/764,870

; Prior application data removed - consult PALM or file wrapper

; NUMBER OF SEQ ID NOS: 646

; SOFTWARE: PatentIn Ver. 2.0

; SEQ ID NO 488

; LENGTH: 222

; TYPE: PRT

; ORGANISM: Homo sapiens

US-09-764-870-488

Query Match

Best Local Similarity 80.6%; Score 247.5; DB 9; Length 222;

Matches 50; Conservative 4; Mismatches 3; Indels 5; Gaps 1;

Qy 5 LSLILLVC-----EATWNSGSGNTLENGYPLSRKKNHSOPTQSLDSTPTKAVKT 59

Db 83 LCLVILVAVVLTGTMAIWRNSGSGNTLENGYPLSRKKNHSOPTQSLDSTPTKAVKT 142

Qy 60 TG 61

Db 143 TG 144

Search completed: June 1, 2004, 08:19:58
Job time : 53 secs